IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Weers et al. Application No: 10/751,342 Confirmation No: 7605 Filed: December 31, 2003 Title: AEROSOLIZABLE PHARMACEUTICAL FORMULATION FOR FUNGAL INFECTION THERAPY	Group Art Unit: 1617 Examiner: Carter, Kendra D Attorney Docket No: 53311-US-CNT (NV.0190.00) November 24, 2010 San Francisco, California

APPEAL BRIEF

VIA EFS

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Examiner:

In response to the Examiner's Final Rejection of May 24, 2010 and the Notice of Appeal filed on September 24, 2010, the Applicant of the above-referenced patent application (hereinafter Appellant) hereby appeals to the Board of Patent Appeals and Interferences. Appellant requests the reversal of the Final Rejection.

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By: Melanie Hitchcock
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Date: November 24, 2010

(1) *Real Party in Interest*

The real party in interest of the present application is Novartis AG (by way of assignment from Novartis Pharmaceuticals AG and from Nektar Therapeutics, which was formerly Inhale Therapeutic Systems, Inc.), having a place of business at Forum 1, Novartis Campus, CH-4056 Basel, Switzerland.

(2) *Related Appeals and Interferences*

Appellant, Appellant's legal representative, and assignee are aware of no appeals or interferences which will directly affect or be directly affected by or have a bearing on the Board's decision in the present appeal.

(3) *Status of Claims*

Claims 1-15, 18-20, 23-25, 28-31, 38-40, 63-78, 98, 99 and 101 are presently pending in the case. Claims 1-15, 18-20, 23-25, 28-31, 38-40, 63-78, 98, 99 and 101 have been finally rejected. The rejection of each of claims 1-15, 18-20, 23-25, 28-31, 38-40, 63-78, 98, 99 and 101 is hereby appealed.

Claims 16, 17, 21, 22, 26, 27, 32-37, 41-62, 79-97 and 100 have been cancelled.

(4) *Status of Amendments*

No amendments have been filed after Final Office Action. Accordingly, all amendments submitted during prosecution have been entered.

(5) *Summary of the Claimed Subject Matter*

As recited in claim 1, a method of providing therapy against a pulmonary fungal infection (page 7 lines 14-17) comprises determining a minimum inhibitory concentration of an antifungal agent for inhibiting a specific pulmonary fungal infection (page 9 lines 5-29) and administering by inhalation directly to the lungs of a patient a powder aerosolized pharmaceutical formulation comprising an antifungal agent (page 7 line 19 through page 8 line 3) having efficacy against said pulmonary fungal infection. The powder comprises porous particles and has a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3 (page 14 through page 25). The powder formulation is administered in a first dosage, followed after a predetermined time interval by a second dosage (page 11 line 16 through page 13 line 10). The first dosage is greater than the second dosage. A sufficient amount of the pharmaceutical formulation is administered to maintain for at least one week a target antifungal lung concentration of at least two times the determined minimum inhibitory concentration (page 10 line 1-14).

As recited in claim 23, a method of providing therapy against a pulmonary fungal infection (page 7 lines 14-17) comprises an aspergillosis comprises administering by inhalation directly to the lungs of a patient an aerosolized pharmaceutical formulation comprising amphotericin B (page 7 lines 19-22). The formulation comprises porous particles having a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3 (page 14 through page 25). A sufficient amount of the pharmaceutical formulation is administered to maintain for at least two weeks a target amphotericin lung concentration of at least 9 µg/g (page 10 lines 1-14). The administration comprises a first administration period and a second administration period and wherein the amphotericin B is administered more frequently or at a higher dosage during the first administration period than during the second administration period (page 11 line 16 through page 13 line 10).

(6) *Grounds of Rejection to be Reviewed on Appeal*

Appellant requests review of the Examiner's following grounds of rejection:

Claims 1-15, 18-20, 23-25, 28-31, 38-40, 63-76, 98, 99 and 101 have been rejected under 35 U.S.C. §103(a) as being unpatentable over US Patent Application 2002/0177562 to Weickert et al (hereinafter Weickert et al) in view of U.S. Patent 6,395,300 to Straub et al (hereinafter Straub et al).

Claims 1-15, 18-20, 23-25, 28-31, 38-40, 98 and 99 have been provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 23-25, 27-30 and 35-44 of copending Patent Application No. 11/187,757 (hereinafter '757 Application).

Claims 77 and 78 have been rejected for unknown reasons.

(7) *Argument*

Appellant believes each of claims 1-15, 18-20, 23-25, 28-31, 38-40, 63-76, 98, 99 and 101 is improperly rejected and is therefore allowable for the following reasons.

<u>The rejections under §103(a) are improper</u>

The Examiner's rejection of claims 1-15, 18-20, 23-25, 28-31, 38-40, 63-76, 98, 99 and 101 under 35 USC §103(a) as being unpatentable over Weickert et al in view of Straub et al is improper and should be reversed.

Independent Claim 1

Independent claim 1 is not rendered unpatentable by Weickert et al and Staub et al. Claim 1 is to a method of providing therapy against a pulmonary fungal infection comprising, *inter alia*, administering by inhalation a powder comprising an antifungal agent, wherein the powder comprises porous particles and has a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3, the powder formulation being administered in a first dosage, followed after a predetermined time interval by a second dosage, said first dosage being greater than the second dosage and wherein a sufficient amount of the pharmaceutical formulation is administered to maintain for at least one week a target antifungal lung concentration of at least two times a determined minimum inhibitory concentration. The references applied by the Examiner fail to teach many of these claimed features.

The Examiner's rejection of claim 1 should be reversed because the references cited and the rationale provided by the Examiner do not properly account for at least three claim limitations in claim 1. Namely, Weickert et al and Shaub et al fail to teach or suggest to one having ordinary skill in the art: (i) maintaining for at least one week an antifungal lung concentration of a least two times the minimum inhibitory concentration; (ii) a treatment regiment where a first dosage is administered for a predetermined time interval followed by second smaller dosage; and (iii) the use of porous particles that have a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3. The references' failure to teach or suggest any one of these features would be enough to justify reversal of the rejection of claim 1. In actuality, the references fail to teach or suggest all three features, as will be explained.

(i) Maintenance of lung concentration as claimed

First, Weickert et al does not disclose or suggest the administration of a sufficient amount of a formulation to maintain for at least one week an antifungal lung concentration of at least two times a determined minimum inhibitory concentration.

Weickert et al only discusses daily administration and does not recognize or teach the benefits of administration in a manner that maintains the claimed level of antifungal agent for the claimed period of time. Unlike that which is claimed by Appellant, Weickert et al merely teaches that an antifungal agent may be administered from 1 to 8 times daily for over seven days and the doses are 3-10 or more times the MIC_{90} (paragraphs 0127 and 0128). However, this Weickert et al administration is not the same as that which Appellant claims in claim 1. Appellant has discovered that it is the ***maintenance*** of a lung concentration of the antifungal agent of at least two times the minimum inhibitory concentration for a period of at least a week that is the most effective treatment. This ***maintenance*** is not appreciated, taught or suggested by the teachings of Weickert et al.

Using the technique of Weickert et al, the lung concentration of antifungal agent could easily fall below the required 2x minimum inhibitory concentration requirement between doses. This is particularly true because many antifungal agents have notoriously low lung residence times. In contrast, Appellant has invented a formulation with sufficiently high lung residence time that allows for the maintenance of desirable lung concentration over a long period of time without the need to bombard the lungs with enormously high concentrations of drug that often will pass immediately into the blood stream with undesirable effects, as described throughout Appellant's specification. It is the discovery and recognition that it is the maintenance of the lung concentration over a period of at least one week that is a significant advancement in the art over the teachings of Weickert et al. Weickert et al's administration technique where the lung concentration of antifungal agent may spike above the 2x minimum inhibitory concentration and then fall below the threshold is neither as effective as Appellant's claimed methodology, nor does it render it unpatentable.

Shaub et al is not relied upon by the Examiner to teach anything related to the maintenance of an antifungal lung concentration at more than two times the minimum inhibitory concentration for at least one week. Since neither reference teaches or suggests this claimed feature, the Examiner has failed to establish a prima facie case

under 35 U.S.C. §103(a), and Appellant requests reversal of the rejection.

(ii) Treatment regimen of a first dosage and a second smaller dosage

Secondly, Weickert et al does not disclose or suggest the administration of a first dosage and then a second dosage less than the first dosage. Appellant has discovered a particularly useful treatment regimen. For example, as shown in Appellant's Figure 3, a first dosage can be administered to achieve a target antifungal concentration in the lungs and then a second smaller dosage can be administered to maintain that concentration. Weickert et al does not teach such a regimen, nor does Staub et al.

In the Final Office Action of May 24, 2010, the Examiner states that Appellant's claimed regimen would have been obvious to one having ordinary skill in the art because Weickert et al teaches that the dosage amount can vary (page 14 lines 14-20 of the Final Office Action). However, as recognized by the Examiner, the variations of dosages are for either the condition being treated and for patient age, weight, etc. In other words, the prescribed dosage might vary from one patient to another. In contast to that which is claimed by Appellant, though, there is no teaching in Weickert et al to vary the dosage for the same patient within the same treatment regimen. The language of claim 1 makes clear that the two-dosage regimen is for the same patient in during the same course of treatment: "the powder formulation being administered in a first dosage, followed after a predetermined time interval by a second dosage, said first dosage being greater than the second dosage and wherein a sufficient amount of the pharmaceutical formulation is administered to maintain for at least one week a target antifungal lung concentration of at least two times a determined minimum inhibitory concentration."

Shaub et al is also not relied upon by the Examiner to teach anything related to the first and second dosages. Since neither reference teaches or suggests this claimed feature, the Examiner has for this additional reason failed to establish a prima facie case under 35 U.S.C. §103(a), and Appellant requests reversal of the rejection.

(iii) Porous particles as claimed

Third, Weickert et al does not disclose or suggest porous particles having a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3. The Examiner attempts to make up for this deficiency by concluding that one of ordinary skill in the art would have found it obvious to use the particles taught by Staub et al in place of the particles of Weickert et al. The Examiner's conclusion is improper. Staub et al teaches the incorporation of a porous matrix for the purpose of enhancing dissolution of a drug. Nowhere does Weickert et al teach that dissolution of a drug is an issue. Thus, one of ordinary skill in the art would not have been motivated to modify the teachings of Weickert et al to achieve an enhanced dissolution. Therefore, there would have been no reason for one of ordinary skill in the art to have combined the teachings of Staub et al with the teachings of Weickert et al in a manner that would arrive at the invention as set forth in Appellant's claim 1.

Furthermore, one of ordinary skill in the art would have been steered away from making the Examiner's proposed modification. If one were to enhance the dissolution of a drug, its lung retention properties would be decreased, making it more difficult to maintain a concentration in the lungs for a long period of time. This would increase the necessary dosages and frequency of dosing, both of which would be undesirable to one having ordinary skill in the art.

Moreover, the particles that would result from the Examiner's proposed modification would not read on the claim 1 particles. The Staub et al particles are not disclosed to have a bulk density of less than 0.5 g/cm^3. Thus, even if one of ordinary skill in the art were to modify Weickert et al by substituting the particles of Staub et al, the resulting particles would not satisfy the limitations of claim 1. Accordingly, claim 1 is not rendered unpatentable by the proposed modification, even if it were made.

Conclusion of obviousness

For at least the reasons discussed above, claim 1 is not properly rejectable under 35 USC §103(a) as being unpatentable over Weickert et al and Staub et al. Aside from the fact that all features are not accounted for by the Examiner, the modification proposed by the Examiner to arrive at Appellant's claimed particles is not one that would have been well within the grasp of one of ordinary skill in the art at the time the invention was made. In this regard, the Examiner has failed to establish that the teachings of Staub et al could be applied, with a reasonable likelihood of success, to Weickert et al, and if they were, if the resulting combination would meet the limitations of the claim. There is no evidence to suggest that this is a situation where the ordinary artisan could have combined in the teachings in a manner that would result in the invention of claim 1, and there is no evidence to suggest the artisan would have seen the benefit in doing so.

Furthermore, any conclusion of obviousness would be clearly negated by Appellant's unexpected discovery. Appellant has unexpectedly found that by administering in the manner claimed, a more effective and safer therapy against fungal infections can be provided. Thus, claim 1 is allowable over the references cited.

Appellant requests reversal of the rejection of claim 1 under 35 U.S.C. §103(a). In addition, Appellant requests reversal of the rejection of claims 2-15, 18-20, 63-76, 98 and 99 which depend from claim 1 and are not rendered unpatentable by Weickert et al and Staub et al for at least the same reasons as claim 1.

Independent claim 23

Weickert et al and Staub et al do not render independent claim 23 unpatentable either. Claim 23 is to a method of providing therapy against a pulmonary fungal infection comprising an aspergillosis, the method comprising administering by inhalation directly to the lungs of a patient an aerosolized pharmaceutical formulation comprising

amphotericin B, wherein the formulation comprises porous particles characterized by a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3, and wherein a sufficient amount of the pharmaceutical formulation is administered to maintain for at least two weeks a target amphotericin lung concentration of at least 9 µg/g, and wherein the administration comprises a first administration period and a second administration period and wherein the amphotericin B is administered more frequently or at a higher dosage during the first administration period than during the second administration period.

Weickert et al and Staub et al do not teach or suggest the treatment of a pulmonary infection in the manner recited. More specifically, Weickert et al and Staub et al do not teach or suggest the maintenance of an amphotericin lung concentration of at least 9 µg/g for at least two weeks. Weickert et al and Straub et al also do not teach or suggest a first administration period and a second administration period, as discussed above in connection with claim 1. Additionally, Weickert et al and Shaub et al are not properly combinable in a manner that would result in particles of the typed claimed by Appellant in claim 23, as discussed above in connection with claim 1.

For at least these reasons, claim 23 is not properly rejectable under 35 USC §103(a) as being unpatentable over Weickert et al and Staub et al.

Appellant requests reversal of the rejection of claim 23 under 35 U.S.C. §103(a). In addition, Appellant requests reversal of the rejection of claims 24, 25, 28-31, 38-40 and 101 which depend from claim 23 and are not rendered unpatentable by Weickert et al and Staub et al for at least the same reasons as claim 23.

Provisional Double Patenting Rejection

The Examiner provisionally rejected claims 1-15, 18-20, 23-25, 28-31, 38-40, 98 and 99 under the judicially created doctrine of double patenting as being unpatentable over claims 23-25, 27-30, 35-44 of U.S. Patent Application Serial No. 11/187,757 in

view of Straub et al.

Since the claims have not been officially indicated as being otherwise in condition for allowance, a response to the Double Patenting rejection at this time would be premature. Therefore, the Appellant is holding such response in abeyance until such time as the claims are indicated allowable but for the Double Patenting issue.

Claims 77 and 78

Claims 77 and 78 have been indicated as being rejected by the Examiner (see Final Office Action page 1 and page 16), but the Examiner has not provided any reasoning for the rejection. The claims are believed to be allowable at least for depending from an allowable claim, as discussed above. Appellant requests reversal of the rejection.

Conclusion

Thus, it is believed that all rejections made by the Examiner have been addressed and overcome by the above arguments. Therefore, all pending claims are allowable. A reversal is respectfully requested.

Should there be any questions, Appellant's representative may be reached at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES

Dated: November 24, 2010

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(8) Claims Appendix

1. A method of providing therapy against a pulmonary fungal infection, the method comprising:

determining a minimum inhibitory concentration of an antifungal agent for inhibiting a specific pulmonary fungal infection; and

administering by inhalation directly to the lungs of a patient a powder aerosolized pharmaceutical formulation comprising an antifungal agent having efficacy against said pulmonary fungal infection, wherein the powder comprises porous particles and has a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3, the powder formulation being administered in a first dosage, followed after a predetermined time interval by a second dosage, said first dosage being greater than the second dosage;

wherein a sufficient amount of the pharmaceutical formulation is administered to maintain for at least one week a target antifungal lung concentration of at least two times the determined minimum inhibitory concentration.

2. A method according to claim 1 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the epithelial lining of the lung.

3. A method according to claim 1 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the solid tissue of the lungs.

4. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least two weeks.

5. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least three weeks.

6. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least one month.

7. A method according to claim 1 wherein the target antifungal agent lung concentration is maintained for at least three months.

8. A method according to claim 1 wherein the administration comprises delivering a single dose of the pharmaceutical formulation during the first week of administration.

9. A method according to claim 1 wherein the administration comprises delivering at least two doses of the pharmaceutical formulation during the first week of administration.

10. A method according to claim 1 wherein the administration comprises a first administration and a second administration period and wherein the antifungal agent is administered more frequently or at a higher dosage during the first administration period than during the second administration period.

11. A method according to claim 1 wherein the antifungal agent is amphotericin B.

12. A method according to claim 11 wherein the target antifungal lung concentration is at least 9 μg/g.

13. A method according to claim 11 wherein the target antifungal lung concentration is a range of concentrations from 4.5 μg/g to 20 μg/g and wherein the administration comprises delivering the pharmaceutical formulation periodically to maintain the antifungal agent lung concentration within the target antifungal lung concentration range.

14. A method according to claim 13 wherein the target antifungal lung concentration is from 9 to 15 μg/g.

15. A method according to claim 1 wherein the antifungal agent comprises one or more of amphotericin B, nystatin, hamycin, natamycin, pimaricin, ambruticin, acrisocin, aminacrine, anthralin, benanomicin A, benzoic acid, butyloparaben, calcium unidecyleneate, candicidin, ciclopirox olamine, cilofungin, clioquinol, clotrimazole, ecaonazole, flucanazole, flucytosine, gentian violet, griseofulvin, haloprogrin, ichthammol, iodine, itraconazole, ketoconazole, voriconazole, miconazole, nikkomycin Z, potassium iodide, potassium permanganate, pradimicin A, propylparaben, resorcinol, sodium benzoate, sodium propionate, sulconazole, terconazole, tolnaftate, triacetin, unidecyleneic acid, monocyte-macrophage colony stimulating factor (M-CSF), zinc unidecylenateand, and pharmaceutically acceptable derivatives and salts thereof.

18. A method according to claim 1 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

19. A method according to claim 18 wherein the matrix material comprises one or more phospholipids.

20. A method according to claim 1 wherein the administration comprises delivering the pharmaceutical formulation in dry powder form using a dry powder inhaler.

23. A method of providing therapy against a pulmonary fungal infection comprising an aspergillosis, the method comprising:

administering by inhalation directly to the lungs of a patient an aerosolized pharmaceutical formulation comprising amphotericin B, wherein the formulation comprises porous particles having a mass median aerodynamic diameter of less than about 5 microns and a bulk density of less than about 0.5 g/cm^3, and

wherein a sufficient amount of the pharmaceutical formulation is administered to maintain for at least two weeks a target amphotericin lung concentration of at least 9 μg/g, and wherein the administration comprises a first administration period

and a second administration period and wherein the amphotericin B is administered more frequently or at a higher dosage during the first administration period than during the second administration period.

24. A method according to claim 23 wherein the amphotericin B concentration is the concentration in the epithelial lining of the lung.

25. A method according to claim 23 wherein the amphotericin B concentration is the concentration in the solid tissue of the lung.

28. A method according to claim 23 wherein the target amphotericin B lung concentration is maintained for at least one month.

29. A method according to claim 23 wherein the target amphotericin B lung concentration is maintained for at least three months.

30. A method according to claim 23 wherein the administration comprises delivering a single dose of the pharmaceutical formulation during the first week of administration.

31. A method according to claim 23 wherein the administration comprises delivering at least two doses of the pharmaceutical formulation during the first week of administration.

38. A method according to claim 23 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

39. A method according to claim 38 wherein the matrix material comprises one or more phospholipids.

40. A method according to claim 23 wherein the administration comprises delivering the pharmaceutical formulation in a dry powder form using a dry powder inhaler.

63. A method according to claim 1, further comprising administering an immunosuppressive agent to the patient for a period of time; and

maintaining the target antifungal agent lung concentration throughout the period of time.

64. A method according to claim 63 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the epithelial lining of the lung.

65. A method according to claim 63 wherein the minimum inhibitory concentration is the minimum inhibitory concentration in the solid tissue of the lung.

66. A method according to claim 63 wherein the administration comprises delivering at least two doses per week of the pharmaceutical formulation before the administration of the immunosuppressive agent and wherein the target concentration is maintained by administering doses of the pharmaceutical formulation less frequently.

67. A method according to claim 63 wherein the antifungal agent is amphotericin B.

68. A method according to claim 67 wherein the target antifungal lung concentration is at least 4.5 μg/g.

69. A method according to claim 67 wherein the target antifungal lung concentration is a range of concentrations from 4.5 μg/g to 20 μg/g and wherein the administration comprises delivering the pharmaceutical formulation periodically to maintain the antifungal agent lung concentration within the target antifungal lung concentration range.

70. A method according to claim 67 wherein the target antifungal lung concentration is from 9 to 15 μg/g.

71. A method according to claim 63 wherein the antifungal agent comprises one or more of amphotericin B, nystatin, hamycin, natamycin, pimaricin, ambruticin, acrisocin, aminacrine, anthralin, benanomicin A, benzoic acid, butyloparaben, calcium unidecyleneate, candicidin, ciclopirox olamine, cilofungin, clioquinol, clotrimazole, ecaonazole, flucanazole, flucytosine, gentian violet, griseofulvin, haloprogrin, ichthammol, iodine, itraconazole, ketoconazole, voriconazole, miconazole, nikkomycin Z, potassium iodide, potassium permanganate, pradimicin A, propylparaben, resorcinol, sodium benzoate, sodium propionate, sulconazole, terconazole, tolnaftate, triacetin, unidecyleneic acid, monocyte-macrophage colony stimulating factor (M-CSF), zinc unidecylenateand, and pharmaceutically acceptable derivatives and salts thereof.

72. A method according to claim 63 wherein the pharmaceutical formulation has a bulk density of less than 0.1 g/cm^3.

73. A method according to claim 63 wherein the pharmaceutical formulation comprises hollow and/or porous particles.

74. A method according to claim 63 wherein the pharmaceutical formulation comprises particles comprising the antifungal agent and a matrix material.

75. A method according to claim 74 wherein the matrix material comprises one or more phospholipids.

76. A method according to claim 63 wherein the administration comprises delivering the pharmaceutical formulation in dry powder form using a dry powder inhaler.

77. A method according to claim 63 wherein the pharmaceutical formulation comprises a propellant and wherein the administration comprises aerosolizing the antifungal agent by opening a valve to release the pharmaceutical formulation.

78. A method according to claim 63 wherein the pharmaceutical formulation is a liquid and wherein the administration comprises aerosolizing the liquid using a compressed gas and/or a vibrating member.

98. A method according to claim 1 wherein the fungal infection comprises aspergillosis, blastomycosis, disseminated candidiasis, coccidioidomycosis, cryptococcocis, histoplasmosis, mucormycosis, sporotrichosis and combinations thereof.

99. A method according to claim 63 wherein the fungal infection comprises aspergillosis, blastomycosis, disseminated candidiasis, coccidioidomycosis, cryptococcocis, histoplasmosis, mucormycosis, sporotrichosis and combinations thereof.

101. A method according to claim 23 wherein two days following administration, a concentration of antifungal agent in the lungs is at least about 150 times a concentration of amphotericin B in the lungs when delivered intravenously, and wherein a concentration of amphotericin B in the serum is substantially zero.

(9) Evidence Appendix

none

(10) Related Proceedings Appendix

none